

Effect of GnRH agonist and letrozole treatment in women with recurrent implantation failure

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Objective: To compare the influence of dual suppression with the use of GnRH agonist plus aromatase inhibitor compared with suppression with the use of GnRH agonist alone or no suppression at all in patients with idiopathic recurrent implantation failure (RIF).

Design: Retrospective cohort study.

Setting: University-affiliated reproductive center.

Patient(s): A total of 523 infertile women who failed two blastocyst transfers underwent a third frozen blastocyst transfer. Women with known endometriosis were excluded.

Intervention(s): A total of 204 subjects were not pretreated, 143 received 2 months of GnRH agonist (3.75 mg intramuscular leuprolide acetate monthly) only, and 176 received GnRH agonist and aromatase inhibitor (5 mg oral letrozole daily for 60 days). Demographic and stimulation information was collected and cycle outcomes reported.

Main Outcome Measure(s): Clinical pregnancy rates.

Result(s): Age, antral follicle count, basal FSH levels, duration of infertility, previous pregnancies, and full-term deliveries were similar ($P > .05$). Clinical pregnancy rates were higher among women who received GnRH agonist plus letrozole compared with women who received GnRH agonist only or women without pretreatment (63%, 42%, and 40%, respectively; $P < .0001$). Live birth rates were higher among women who received GnRH agonist plus letrozole compared with the other groups (56%, 36%, and 34%; $P < .0001$). No differences in pregnancy outcomes were noted between patients who did not receive pretreatment and those in the GnRH agonist only group.

Conclusion(s): In patients with RIF, treatment with a GnRH agonist plus letrozole may improve live birth rates in subsequent cycles. We hypothesize that this improvement is due to alterations in the endometrium receptivity or treatment of undiagnosed endometriosis. (*Fertil Steril*® 2019;112:98–104. ©2019 by American Society for Reproductive Medicine.)

El resumen está disponible en Español al final del artículo.

Key Words: Infertility, endometriosis, GnRH against, aromatase inhibitor, implantation failure

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Recurrent implantation failure (RIF) is a clinical entity which refers to a clinical scenario when implantation has repeatedly failed, usually after in vitro fertilization (IVF). That said, no standardized definition of RIF currently exists (1).

In some studies, RIF is defined as the failure of implantation after two consecutive cycles of IVF, intracytoplasmic sperm injection (ICSI), or frozen embryo replacement cycles when the cumulative number of transferred embryos was no less than four

with the use of cleavage-stage embryos and no less than two with the use of blastocysts. In these cases, all embryos were required to be of good quality and of appropriate developmental stage (2). For the purposes of this manuscript, we use this definition.

The causes of implantation failure are diverse and include different proposed maternal factors such as uterine abnormalities, hormonal or metabolic disorders, infections, immunologic factors, thrombophilias, embryonic aneuploidy, and embryo-quality issues (1). Several therapeutic approaches have been described as options to improve

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the functions of the endometrium, including immunomodulatory agents, local endometrial injury, autologous adipose-derived stem cells, antioxytocin preparations, and others (3).

Similarly, endometriosis, even in a mild stage, may adversely influence both the uterine microenvironment and embryo quality. A meta-analysis by Barnhart et al. pooled data from 22 nonrandomized studies regarding IVF success rates in patients with endometriosis versus control patients without endometriosis. When adjusted for confounding variables, there was a significantly negative association between endometriosis and pregnancy rates, fertilization rates, implantation rates, peak E_2 concentrations, and the number of retrieved oocytes compared with control women (4).

It is possible that undiagnosed endometriosis is the cause of failed ETs (ETs) in some patients. Therefore, treating endometriosis empirically before ET may improve outcomes in women with RIF.

We performed the present study to evaluate a homogeneous group with two failed high-quality blastocyst transfers of single blastocysts undergoing their third transfer of a single high-quality frozen blastocyst. We hypothesized that before IVF, patients with idiopathic RIF who may have undiagnosed endometriosis might benefit from long-term down-regulation with the use of a GnRH agonist plus an aromatase inhibitor (AI) or with single-agent suppression with the use of a GnRH agonist alone compared with no pretreatment.

MATERIALS AND METHODS

We performed a retrospective cohort study of patients with RIF treated from June 2013 to September 2017 at a single university-affiliated IVF center. Patients empirically treated with GnRH agonist alone or GnRH agonist + letrozole before their third ETs were analyzed. This cohort was compared with women during the same time period with RIF that did not receive the GnRH agonist nor letrozole pretreatment. Individual treatment protocols were decided at the discretion of the treating physician based on the patient's medical history and her physician's experience. Four physicians were involved in patient care during this time period. Three physicians did not pretreat their patients, who were used as the control group without pretreatment. One physician allotted his patients into either the GnRH agonist alone group or the GnRH agonist + letrozole group. This was done to match the maternal age and antral follicle count in each of the two groups. These parameters were added to the mean of these parameters in each group to determine which caused the least disturbance, and as such the patients were allotted to that group. Institutional Review Board authorization was obtained to evaluate the data (no. 2019-5168).

This was a university-based practice consisting of four attending physicians and a Royal College-approved fellowship training program. We cross-cover each other's patients for ET. Clinical and laboratory protocols are recorded and were the same for all physicians, including estrogens used for endometrial support, luteal-phase progesterone replacement, ultrasound-guided ET technique, and transfer catheter used. Attending physician and fellow ET pregnancy rates were monitored and did not differ significantly.

The inclusion criteria were the following: women <40 years of age with documented infertility, a history of three ETs where the first two high-quality blastocyst ETs did not result in pregnancy, and documentation of a normal uterine cavity. Exclusion criteria included women with known endometriosis or endometriomas at surgery or ultrasound, ultrasound findings consistent with adenomyosis, severe male-factor infertility, uterine polyps, fibroids, or hydrosalpinges that had not been removed. All women had normal thyroid function testing, serum prolactin levels, hysteroscopy, and coagulation studies.

A total of 523 infertile women meeting the inclusion criteria were included. All women received a Gardner grade (5) AA, BA, AB, or BB blastocyst, according to post-thaw evaluation. All of the women underwent a single-blastocyst transfer per local government regulations. All women had collected at least three high-quality blastocysts from their first oocyte collection. Sequential single-blastocyst transfer had been performed on all women.

We divided the patients according to the type of treatment received before their third ET. Group 1 received no pretreatment. Group 2 received GnRH agonist alone with two intramuscular injections of 3.75 mg depot leuprolide acetate (Lupron Depot; Abbvie) administered 30 days apart. The first injection was administered during the early follicular phase of the menstrual cycle. Group 3 received GnRH agonist exactly as group 2 plus 5 mg oral letrozole (Femara; Novartis) daily for 60 days concurrently with the GnRH agonist treatment. In groups 2 and 3, the frozen-embryo replacement cycle (FERC) protocol was begun 60 days after the first GnRH agonist injection, which was 30 days after the second GnRH agonist injection. The patients took E_2 valerate (Estrace; Teva North America; 2 mg orally three times daily) for at least 10 days, and then progesterone was added (Endometrin; Ferring; 100 mg vaginally twice daily) when the endometrial thickness was >8 mm. Embryo transfer (ET) was performed on the 6th day of progesterone.

Estrogen and progesterone were continued until a serum β -hCG assay was conducted 11 days after ET. If the hCG assay yielded a positive result, the patient underwent ultrasonographic monitoring to determine fetal viability at approximately the 6th to 7th week of gestation. Estrogen and progesterone supplementation was continued until 12 weeks of gestation. The pregnancy rate was defined by the number of positive of hCG (>20 IU/L) assays 11 days after ET. Clinical pregnancy was defined by the presence of a gestational sac and a live fetus on transvaginal ultrasound as of the 7th week of gestation. Live birth was defined as a live fetus beyond the 24th week of gestation, which was the primary outcome.

Statistical testing was undertaken with the use of SPSS 23.0 (IBM), by means of analysis of variance and Tukey honest statistical difference for post hoc testing for continuous variables and chi-square test for categorical variables. Where appropriate, data are presented as percentages (%) or mean \pm SD. P values $\leq .05$ were considered to be statistically significant. A priori power analysis suggested that ≥ 84 subjects were required in each arm, with a beta error of 0.2 and differences of 40% as extrapolated from our previous

TABLE 1

Patient demographics and clinical characteristics.				
Characteristic	Group 1: no treatment (n = 204)	Group 2: GnRH agonist alone (n = 143)	Group 3: GnRH agonist + letrozole (n = 176)	P Value
Age (y)	35.3 ± 3.2	34.8 ± 3.6	35.2 ± 3.0	.35
AFC	14.6 ± 2.4	14.0 ± 3.4	14.3 ± 2.9	.16
FSH (IU/L)	8.3 ± 1.4	8.2 ± 1.3	8.0 ± 1.4	.10
Previous pregnancies	0.8 ± 0.5	0.7 ± 0.4	0.8 ± 0.6	.14
Previous deliveries	0.6 ± 0.5	0.6 ± 0.5	0.5 ± 0.5	.10
Duration of infertility	2.4 ± 0.9	2.3 ± 1.0	2.5 ± 0.9	.16

Note: None of the post hoc tests were significantly different between any combination of 2 groups (Tukey honest significant difference). AFC = antral follicle count.

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publication (12). To verify results and control for confounding effects, we compared pregnancy outcomes (i.e., clinical pregnancy or live birth: yes or no) and determined if intervention (no pretreatment, GnRH agonist alone, or GnRH agonist + letrozole) was related to different outcomes by means of multivariate stepwise logistic regression. We controlled for antral follicle count (AFC), basal serum FSH levels, duration of infertility, previous pregnancies, previous full-term deliveries, and Gardner grade of the transferred embryo.

RESULTS

Our cohort was divided in the following manner: 204 subjects were not pretreated (group 1), 143 received GnRH agonist only (group 2), and 176 received GnRH agonist + letrozole (group 3). Patient characteristics and demographics are presented in Table 1. No statistical differences were found between the groups regarding age, AFC, basal serum FSH levels, duration of infertility, previous pregnancies, and previous full-term deliveries ($P > .05$). All subjects had a history of two failed blastocyst transfers. Table 2 presents the stimulation characteristics and cycle outcomes of the FERC treatment following the assigned treatment. The total days of stimulation and total dose of gonadotropins and the percentage of ICSI procedures (fresh cycles) were similar. The Gardner grades of the embryos transferred were similar ($P = .38$). Clinical pregnancy rates were significantly higher among women who received GnRH agonist + letrozole (group 3) than among women who received GnRH agonist only (group 2) or women without pretreatment (group 1; 63%, 42%, and 40%, respectively; $P < .0001$). Live birth rates were also significantly higher among the women who received GnRH agonist + letrozole compared with the other two groups (56%, 36%, and 34%, respectively; $P < .0001$). Clinical pregnancy rates and live birth rates were statistically different at the post hoc test (chi-square) between group 1 and group 3 ($P < .0001$) and between group 2 and group 3 ($P < .0001$). None of the other post hoc tests were significantly different.

An analysis was performed with the use of multivariate stepwise logistic regression to control for confounding effects and determine if the allocation was different to each of the pretreatment groups in the groups that did or did not have a clinical pregnancy or live birth. Ideally, multivariate stepwise logistic regression would be done to control for confounding effects. However, three groups cannot be analyzed in that

way. One option is to combine two of the groups, but that has low statistical validity. Therefore, we compared pregnancy outcomes (i.e., clinical pregnancy or live birth: yes or no) and determined if intervention (no pretreatment, GnRH agonist alone, or GnRH agonist + letrozole) was related to different outcomes. We controlled for AFC, basal serum FSH levels, duration of infertility, previous pregnancies, previous full-term deliveries, and Gardner grade of the transferred embryo. Allocation to the three pretreatment groups differed in those with clinical pregnancies (95% confidence interval 1.24–3.45) and live births (1.17–3.56). These results confirmed the detected benefit for the use of GnRH agonist + letrozole in clinical pregnancy and live birth rates when controlling for the listed confounding effects.

DISCUSSION

The presence of RIF poses a challenge for IVF providers. In particular, finding effective treatment modalities to enhance pregnancy and live birth rates remains difficult for providers and patients alike. It is known that inadequate uterine receptivity is responsible for some of the implantation failures, whereas the embryo itself is responsible for the rest. In the present study, our initial hypothesis was that idiopathic RIF patients may have undiagnosed or asymptomatic endometriosis. Diagnostic laparoscopy in North America went out of fashion in the middle to late 1990s. At the time, surgery offered a possible diagnosis of endometriosis, but no treatments were available that could improve outcomes with IVF. In the mid-2000s several randomized controlled trials suggested improved outcomes with IVF when stage III or IV endometriosis was present and patients were pretreated with GnRH agonists for 3–6 months. These findings held up in a meta-analysis (6).

Concomitantly, prolonged administration of GnRH agonists after vitrification of all embryos in IVF patients with advanced endometriosis has been shown to lead to high implantation and ongoing pregnancy rates despite a high incidence of previous cycle failures (7).

Nevertheless, a randomized controlled trial from 2016 did not find any benefit after 3-month adjuvant treatment of mild peritoneal endometriosis with long-acting GnRH agonist after laparoscopic surgery. The control group received long-protocol IVF stimulation, whereas the research group received additional long-acting GnRH agonist for 3 months

TABLE 2

Characteristic	Group 1: no treatment (n = 204)	Group 2: GnRH agonist alone (n = 143)	Group 3: GnRH agonist + letrozole (n = 176)	P Value
Fresh cycle				
Days of stimulation	10.3 ± 3.3	9.8 ± 3.2	9.9 ± 3.3	.31
Gonadotropin dose	2,204 ± 1,246	1,979 ± 1,478	2,018 ± 1,464	.26
Frozen blastocysts	2.9 ± 1.2	2.7 ± 1.4	2.8 ± 0.6	.25
ICSI	79.9% (163/204)	76.2% (109/143)	83.0% (146/176)	.33
FERC treatment following the assigned treatment				
Gardner grade				.38
AA	12% (29)	14% (24)	9% (19)	
AB	28% (68)	31% (53)	28% (59)	
BA	42% (103)	33% (57)	44% (93)	
BB	18% (45)	22% (38)	19% (40)	
Clinical pregnancy rates	40% (82)	42% (60)	63% (111) ^{a,b}	< .0001
Live birth rates	34% (70)	36% (51)	56% (99) ^{a,b}	< .0001

None of the other post hoc tests (not indicated with superscript a or b) were significantly different (chi-square or Tukey honest significant difference, as appropriate). FERC = frozen-embryo replacement cycle; ICSI = intracytoplasmic sperm injection.

^a Post hoc test (chi-square) group 1 vs. group 3: $P < .0001$.

^b Post hoc test (chi-square) group 2 vs. group 3: $P < .0001$.

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before IVF. There was no difference in number of metaphase II oocytes obtained per cycle or pregnancy rate between the groups. In addition, lower doses of FSH and shorter stimulation period were needed to reach adequate follicle maturation in the control group (8). It should be noted that this study was published well after our study had started.

Aromatase inhibitors can also be used to treat endometriosis. AIs reduce local estrogen production, and endometriosis is an estrogen-dependent disease that expresses elevated levels of aromatase compared with normal endometrium. Therefore, AIs are thought to be excellent therapeutic agents for endometriosis (9). Mouse models have shown that AIs can effectively eradicate endometriotic lesions (10).

In a prospective pilot study, Lossel et al. examined the concept of combined down-regulation with the use of an AI and a GnRH agonist before IVF in patients with endometriomas. The primary aim was to study signs of inactivation of the endometriosis during treatment. They found that prolonged combined AI and GnRH agonist down-regulation significantly reduced endometrioma volume and serum CA-125. A high pregnancy and delivery rate was also noted in that uncontrolled study (11).

An initial pilot study comparing GnRH agonist + letrozole versus no pretreatment in patients with multiple unexplained failed ETs showed a significant improvement in live birth rates in the agonist + letrozole group (12). However, the group was heterogeneous, including fresh and frozen ETs, cleavage and blastocyst transfers, and different numbers of previously failed transfers.

The dual treatment with GnRH agonist and AI has another advantage. Treatment with GnRH agonist alone is associated with a flare-up phenomenon. Injection of the GnRH agonist causes an initial rise of gonadotropins which induces an increase in estrogen production lasting for 7–14 days. The elevation in estrogen concentrations may cause unwanted side-effects, including worsening any endometriosis symptoms. However, a preliminary study demonstrated that

AIs are capable of preventing the estrogen increase due to the gonadotropin flare in patients treated with GnRH agonists (13).

However, in the current era, many patients forego diagnostic laparoscopy and go undiagnosed for endometriosis when infertility is the presenting complaint. In the present study, it was initially hypothesized that patients might have better outcomes with long-term down-regulation with the use of GnRH agonist + AI or with the use of GnRH agonist alone compared with no treatment at all before ET. It also could be hypothesized that had advanced endometriosis been present, we would have expected ultrasound findings indicating this diagnosis in some subjects. Therefore, it seems likely that if endometriosis was present, it was mild or moderate (stage I or II), particularly because women with clinical findings consistent with endometriosis were excluded from this study. After analysis, we found that patients with a history of two previous failed ETs performed better with a combination of GnRH agonist + AI, but not with GnRH agonist alone, before ET. This finding is consistent with the possibility of GnRH agonist + AI being an effective treatment for endometriosis (11), whereas GnRH agonist alone seems to be poor treatment for mild and moderate endometriosis.

In contrast to our findings, in a retrospective study of 21 subjects, Yang et al. demonstrated that long-term GnRH agonist treatment alone might be beneficial for patients with idiopathic RIF. They showed that hormonally controlled endometrial preparation with previous GnRH agonist suppression could be used in patients who had experienced repeated failures of IVF treatment despite having morphologically optimal embryos (endometriosis patients were excluded from the study). They suggested that treatment with a GnRH agonist may help to increase the receptivity of the endometrium in those patients (2). Those results occurred in a much smaller sample than that in our study, which may account for the differences.

Several possibilities exist for why no improvement was seen in the GnRH agonist alone group. The first is that treatment of endometriosis is not the cause of improvement. The second possibility is that 2 months of GnRH agonist pretreatment is insufficient to demonstrate an improvement in IVF outcomes when endometriosis is present. Indeed, all randomized studies in the literature used 3–6 months of GnRH agonist suppression. However, the added benefit of adding an AI may be sufficient to obtain improvement in the endometriosis with 2 months of treatment. The third possibility is that the subjects had mild or moderate endometriosis, given that the randomized controlled trial by Decler et al. failed to find improvement in pregnancy outcomes when pretreating mild endometriosis patients with the use of long-acting GnRH agonist compared with no pretreatment (8). It will require further study to determine if treatment with GnRH agonist + AI improves outcomes in mild and moderate endometriosis patients before ET compared with no pretreatment. The last possibility is that the AI alone contributed to the outcomes and not the GnRH agonists.

The concept of dual suppression (GnRH agonist + AI) before IVF has an appealing biologic plausibility through the additional blockade of extraovarian aromatase receptors aberrantly expressed in endometriotic implants as well as the eutopic endometrium of women with endometriosis (14, 15).

Lossl et al. demonstrated that dual suppression prior to IVF reduces endometrioma volume and serum CA-125 and may thus result in a higher pregnancy rate. However, in their study, a comparable suppression with GnRH agonist alone was not undertaken, so it is difficult to assess the effect of the addition of an AI agent (11).

Another potential mechanism to explain the findings is the correction of possible aberrant integrin expression. Integrins are a family of transmembrane glycoproteins formed by the association of α and β subunits. A large variety of integrins have been described, and low integrin expression has been described in cases of unexplained IVF failure (16), whereas positive integrin expression is predictive of future IVF success (17). $\beta 3$ -Integrin has been characterized as a biomarker of uterine receptivity in humans, and the $\alpha v \beta 3$ integrin has been described as a predictor of IVF success (17–21). It is also known that aberrant $\alpha v \beta 3$ integrin expression has been associated with unexplained infertility (16, 22, 23). Recently, in a retrospective cohort study, Surrey et al. demonstrated that prolonged administration of GnRH agonist after vitrification of all embryos in IVF patients with endometriosis and/or aberrant endometrial integrin expression led to high implantation and ongoing pregnancy rates despite a high incidence of previous cycle failures (7). In a murine model with decreased endometrial $\beta 3$ -integrin, uterine receptivity resulting from ovarian stimulation was partially restored after GnRH agonist administration (24).

In a retrospective study, Miller et al. examined the relationship between $\alpha v \beta 3$ integrin and IVF outcomes in women who did or did not receive letrozole treatment during the IVF cycle stimulation. Women undergoing IVF with low integrin expression had significantly reduced implantation

and pregnancy rates compared with women with normal integrin expression. In those women who underwent IVF with low integrin expression who received letrozole, the pregnancy rate was similar to women with normal integrin expression. Based on the findings, they concluded that letrozole improved integrin expression along with implantation and pregnancy rates, and it might be a useful adjunct therapy during IVF protocols, especially in women with unexplained IVF failure or endometriosis (25).

Given the significantly improved understanding of the mechanisms of action of AIs and GnRH agonists, respectively, and the mechanisms of combination treatment, the association of an AI and a GnRH agonist may be therapeutic in some RIF patients. GnRH agonists can decrease estrogen synthesis from the gonads, and AIs can inhibit the synthesis of estrogens from local and peripheral tissue so that the combined administration of AI and GnRH agonist can block estrogen more deeply and both of them together may improve integrin expression.

It is important to mention that the side-effect of prolonged treatment with GnRH agonists have to be taken into account. Although generally well tolerated, some women experience vasomotor instability and other symptoms of hypoestrogenism, such as an acceleration of bone loss. This may increase future fractures or osteoporosis rates (26).

It could be hypothesized that because no improvement was seen with the GnRH agonist alone whereas the combination of GnRH agonist and letrozole resulted in better outcomes, that the benefit is due to the letrozole alone. This could be true, but its use alone involves several logistical difficulties, including superovulation and ovarian cyst development producing hormones and delaying ET. A future study could compare results with the use of letrozole and birth control pills or progestin.

This study has a number of strengths. It is the first that compares the use of dual suppression of GnRH agonist + AI compared with suppression by GnRH agonist alone or no suppression in idiopathic RIF patients. The number of patients was high, and there were no significant differences between the groups in terms of demographics and clinical characteristics.

However, this study also has several weaknesses. It was a retrospective cohort and not a prospective randomized study; as such, undetected biases may be present. This was not an intention-to-treat analysis in that subjects with embryos which failed to survive thawing or that were Gardner grade C (in the inner cell mass or trophectoderm grade) or less after thawing were not included in the analysis. This is likely both a strength and a weakness. Had these subjects been included, it may have masked the benefit of the pretreatment, particularly if they were not equally distributed.

In conclusion, this study showed that endometrial preparation with the use of a GnRH agonist plus an AI may be used to improve outcomes for patients who have experienced RIF in IVF-ET treatment despite having morphologically optimal embryos. However, pretreatment with GnRH agonist alone does not seem to improve outcomes for RIF. This should be confirmed in a prospective randomized study.

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Efecto del tratamiento con agonista de la GnRH y letrozole en mujeres con fallo de implantación recurrente

Objetivo: Comparar la influencia de la supresión dual con el uso del agonista de la GnRH y el inhibidor de la aromatasa en comparación con la supresión con el agonista de la GnRH solo o sin supresión en pacientes con fallo de implantación recurrente (RIF) idiopática.

Diseño: Estudio de cohortes retrospectivo.

Ámbito: Centro reproductivo afiliado a la Universidad.

Paciente(s): Un total de 523 mujeres infértiles que fallaron en dos transferencias de blastocisto y se sometieron a una tercera transferencia de un blastocisto congelado. Mujeres con endometriosis conocida fueron excluidas.

Intervención(es): Un total de 204 sujetos no fueron pretratados, 143 recibieron durante 2 meses solo agonista de la GnRH (3,75 mg de acetato de leuprolide intramuscular mensualmente), y 176 recibieron agonistas de GnRH e inhibidor de aromatasa (5 mg de letrozole oral diariamente durante 60 días). Se recogió la información demográfica, así como de la estimulación y los resultados de los ciclos fue reportada.

Principal(es) medida(s) de resultado: Tasas clínicas de gestación.

Resultado(s): Edad, número de folículos antrales, niveles de FSH basales, duración de la esterilidad, gestaciones previas, y gestaciones a término fueron similares ($p > 0,05$). Las tasas clínicas de gestación fueron mayores en las mujeres que recibieron agonista de GnRH junto con letrozole comparado con las mujeres que recibieron sola el agonista de GnRH o las mujeres sin pretratamiento (63%, 42%, y 40%, respectivamente; $p < 0,0001$). Las tasas de nacido vivo fueron mayores en las mujeres que recibieron agonista de GnRH junto con el letrozole comparado con los otros grupos (56%, 36%, y 34%; $p < 0,0001$). No se observaron diferencias en cuanto a los resultados de embarazo entre el grupo de pacientes que no recibió pretratamiento y aquellas que recibieron solo el agonista GnRH.

Conclusión(es): En pacientes con RIF, el tratamiento con agonista de la GnRH junto con letrozole puede mejorar las tasas de nacido vivo en ciclos posteriores. Nosotros hipotetizamos que esta mejora se debe a alteraciones en la receptividad endometrial o al tratamiento de la endometriosis no diagnosticada.